

**Radboud Repository**

Radboud University Nijmegen 

## PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/20708>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

# Neural tube defects and elevated homocysteine levels in amniotic fluid

Régine P. Steegers-Theunissen, MD,<sup>a, b</sup> Godfried H. Boers, MD,<sup>c</sup> Henk J. Blom, PhD,<sup>d</sup> Jan G. Nijhuis, MD,<sup>a</sup> Chris M.G. Thomas, PhD,<sup>a</sup> George F. Borm, PhD,<sup>c</sup> and Tom K. Eskes, MD<sup>a</sup>

Nijmegen, The Netherlands

**OBJECTIVE:** Our purpose was to study maternal blood and amniotic fluid concentrations of homocysteine and relevant vitamins in relation to neural tube defects.

**STUDY DESIGN:** Concentrations of total homocysteine, folate, and vitamins B<sub>12</sub> and B<sub>6</sub> were measured in maternal blood and amniotic fluid of 27 women carrying a fetus with a neural tube defect and 31 control women carrying a healthy fetus.

**RESULTS:** The mean total homocysteine concentration in amniotic fluid of the study group was significantly higher than that of the control group. The mean concentrations of total homocysteine in blood and the vitamins folate, B<sub>12</sub>, and B<sub>6</sub> in, respectively, blood and amniotic fluid were not significantly different between the groups. The mean concentrations of homocysteine and vitamin B<sub>6</sub> were significantly lower in amniotic fluid than in blood in both groups, whereas vitamin B<sub>12</sub> in amniotic fluid was higher than in blood.

**CONCLUSION:** These results support the hypothesis that at least the cause of a subset of neural tube defects could reside in a primary or secondary maternal or fetal derangement of homocysteine metabolism. (AM J OBSTET GYNECOL 1995;172:1436-41.)

**Key words:** Neural tube defects, amniotic fluid, maternal blood, homocysteine, vitamins

Decreased levels of folate and vitamin B<sub>12</sub> in maternal blood have been associated with the pathogenesis of neural tube defects.<sup>1, 2</sup> Periconceptional folate treatment of the mother is very likely to prevent neural tube defects.<sup>3, 4</sup> Recently we reported an association between a history of offspring with a neural tube defect and maternal mild hyperhomocysteinemia in the fasting state and after methionine loading.<sup>5, 6</sup> However, it is unclear what biochemical mechanism is involved, but probably the underlying defect is located in the remethylation pathway of homocysteine metabolism.

5-Methyltetrahydrofolate and B<sub>12</sub> as methylcobalamin are involved in the remethylation of homocysteine to methionine. Vitamin B<sub>6</sub> as pyridoxal phosphate is involved in the competing transsulfuration pathway, which degrades homocysteine by cystathionine into cysteine. Malnutrition or a deranged metabolism of folate or vitamin B<sub>12</sub> impairs the remethylation to methionine and results in hyperhomocysteinemia.<sup>7-9</sup> The most fre-

quently encountered inherited enzymatic defects in homocysteine metabolism are deficiencies of the enzymes cystathionine synthase and 5,10-methylenetetrahydrofolate reductase.<sup>9</sup> Noteworthy is the recently reported decreased enzyme activity of a thermolabile form of 5,10-methylenetetrahydrofolate reductase, which may result in mild hyperhomocysteinemia in 5% of the general population.<sup>10</sup> Increased homocysteine blood levels can be efficiently lowered by high-dose folate or vitamin B<sub>6</sub>.<sup>11, 12</sup>

In view of the previously reported association of maternal hyperhomocysteinemia and offspring with a neural tube defect, it would be intriguing to study the homocysteine exposure of the conceptus during the period that neural tube defects develop (i.e., third to fourth week after conception). However, it is not feasible to assess the homocysteine concentrations in the yolk sac, in the neural tissue, or even in amniotic fluid during that early stage of human pregnancy. Therefore we studied both maternal blood and midtrimester amniotic fluid concentrations of total homocysteine, folate, and vitamins B<sub>12</sub> and B<sub>6</sub> in women carrying a fetus with a neural tube defect and in a control group of women carrying a normal, healthy fetus.

## Material and methods

Fifty-eight women were investigated after written informed consent was obtained. Exclusion criteria were gastrointestinal and endocrine disorders, dietary re-

*From the Departments of Obstetrics and Gynecology,<sup>a</sup> Epidemiology,<sup>b</sup> Medicine,<sup>c</sup> Pediatrics,<sup>d</sup> and Medical Statistics,<sup>e</sup> University Hospital St. Radboud.*

*Supported by grants from the Dutch "Praeventiefonds" no 28.1006/1 and Corporate Development International. Received for publication March 14, 1994; revised July 8, 1994; accepted November 7, 1994.*

*Reprint requests: R.P.M. Steegers-Theunissen, MD, Department of Medical Informatics and Epidemiology, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.*

*Copyright © 1995 by Mosby-Year Book, Inc.*

*0002-9378/95 \$3.00 + 0 6/1/61853*

**Table I.** Characteristics of populations

	Group 1 (NTD) (n = 27)	Group 2 (controls) (n = 31)	Significance
Age (yr) (mean and SD)	30.5 (4.2)	37.8 (1.3)	$p < 0.01$
Nulliparous	9	7	NS
Gestational age (wk) (mean and SD)*	22.3 (8.8)	15.9 (0.7)	$p < 0.01$

NTD, Neural tube defect; NS, not significant.

\*At amniocentesis.

**Table II.** Mean and SD amniotic fluid and maternal blood concentrations of total homocysteine and vitamins in women carrying a fetus with a neural tube defect (group 1) and in women with a healthy fetus (group 2)

	Group 1 (NTD) (n = 27)	Group 2 (controls) (n = 31)	Significance between groups
Total homocysteine ( $\mu\text{mol/L}$ )			
Plasma	7.7 (3.2)	7.2 (1.2)	NS
Amniotic fluid	2.6 (1.6)	1.5 (0.4)	$p < 0.01$
Significance within group	$p < 0.01$	$p < 0.01$	
Folate (nmol/L)			
Serum	15 (6)	15 (6)	NS
Amniotic fluid	14 (8)	13 (5)	NS
Significance within group	NS	$p < 0.01$	
Red blood cells	646 (324)	644 (170)	NS
Vitamin B <sub>12</sub> (pmol/L)			
Serum	219 (67)	238 (66)	NS
Amniotic fluid	379 (298)	481 (278)	NS
Significance within group	$p < 0.05$	$p < 0.01$	
Vitamin B <sub>6</sub> (nmol/L)			
Whole blood	41 (11)	41 (14)	NS
Amniotic fluid	20 (19)	14 (13)	NS
Significance within group	$p < 0.01$	$p < 0.01$	

NTD, Neural tube defect; NS, not significant.

strictions, and the use of vitamin preparations or other pharmacologic agents immediately before or during the current pregnancy. Twenty-seven of the women carried a fetus with a neural tube defect (i.e., meningo[myelo]cele [ $n = 15$ ] or anencephaly [ $n = 12$ ] (group 1) as concluded from  $\alpha$ -fetoprotein determinations in amniotic fluid and from ultrasonographic examination and confirmed by the pregnancy outcome. The control group (group two) consisted of 31 women in whom amniocentesis was performed because of high maternal age (36 to 40 years). All control women gave birth to a healthy child. All pregnancies were accurately dated by the last menstrual period and by first-trimester ultrasonographic investigation. The characteristics of both groups are presented in Table I.

Venous blood samples for the determination of plasma total homocysteine, serum and red blood cell folate, serum vitamin B<sub>12</sub>, and whole blood vitamin B<sub>6</sub> as pyridoxal phosphate were taken within 10 minutes after amniocentesis. Amniotic fluid samples were obtained by routine transabdominal amniocentesis and collected in dry tubes of 10 ml. All amniotic fluid samples were free from blood contamination. The samples were immediately centrifuged for 10 minutes at 3000 g, stored at  $-20^\circ\text{C}$ , and assayed within 3 months

after collection. The analytic methods used in the determination of vitamins in blood and amniotic fluid have been reported before.<sup>13</sup> Total homocysteine was determined essentially according to Fiskerstrand et al.<sup>14</sup>

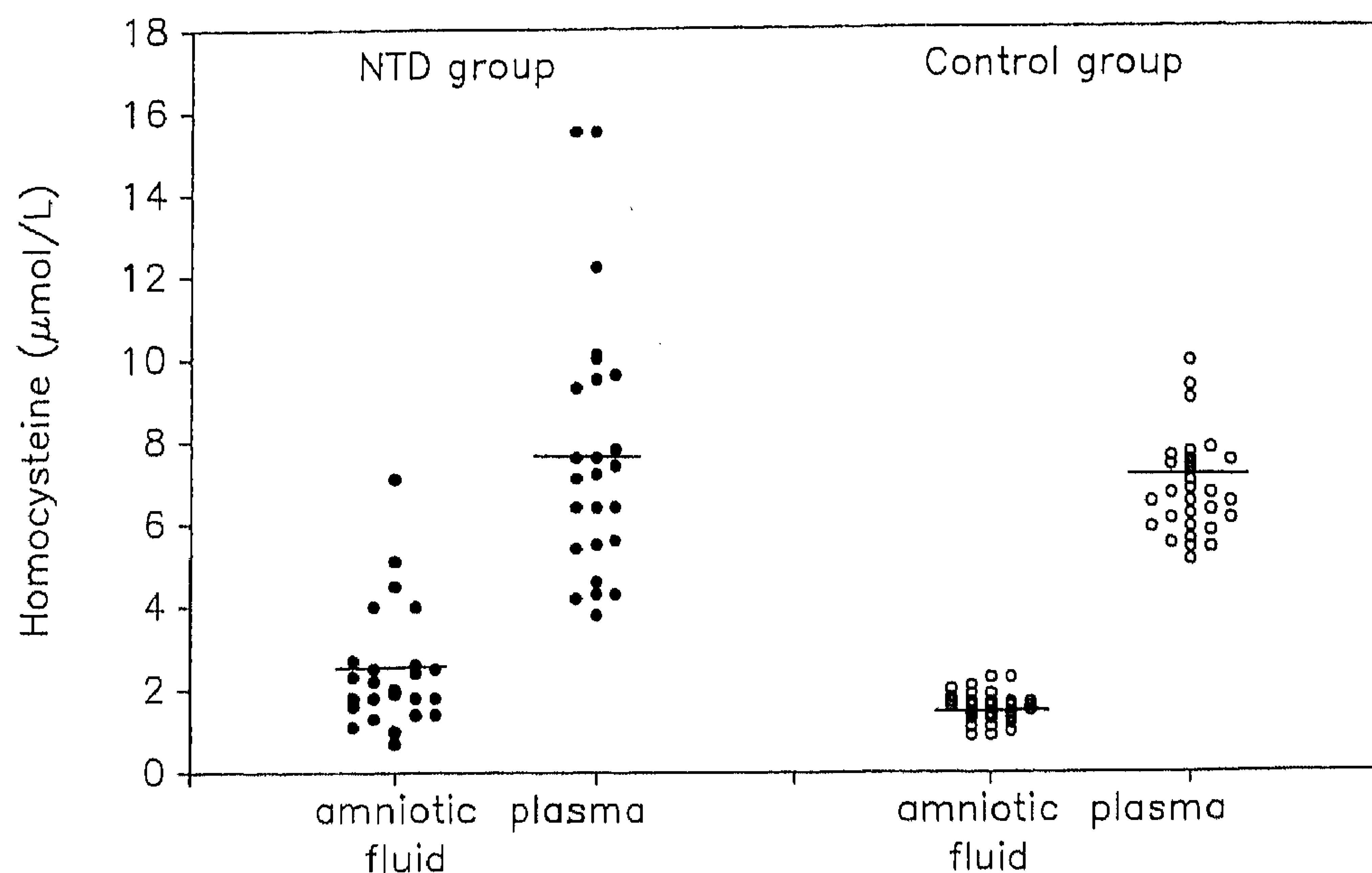
Results are expressed as mean (SD). To obtain normality, blood and amnion parameters were log-transformed. Possible differences between the groups were then evaluated with Welch's  $t$  test, whereas differences between paired observations were validated with the Student  $t$  test. Pearson's partial correlation coefficients (with the group effect partialled out) were calculated to study the relationship between the various variables. A  $p$  value  $< 0.05$  was considered statistically significant.

## Results

Amniocentesis was performed at a significantly more advanced gestational age in group 1 compared with group 2, and the women in group 2 were significantly older than those in group 1 (Table I).

The mean concentrations of total homocysteine, folate, and vitamins B<sub>12</sub> and B<sub>6</sub> in maternal blood and amniotic fluid as found in groups 1 and 2 are given in Table II. The mean amniotic fluid concentration of total homocysteine in group 1 was significantly higher than that of group 2 ( $p < 0.01$ ), whereas these concen-





**Fig. 1.** Individual plasma and amniotic fluid levels of homocysteine in women carrying a fetus with a neural tube defect (NTD) (group 1) and in those carrying a healthy fetus (group 2). Horizontal rule, Mean.

**Table III.** Partial correlation coefficients of concentrations of total homocysteine in both plasma and amniotic fluid with concentrations of folate, vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, and gestational and maternal age

	Total homocysteine			
	Plasma	Significance	Amniotic fluid	Significance
Maternal age	-0.07	NS	-0.04	NS
Gestational age	-0.35	$p < 0.05$	-0.05	NS
Total homocysteine				
Plasma	—		0.45	$p < 0.01$
Folate				
Serum	-0.46	$p < 0.01$	-0.36	$p < 0.01$
Red blood cells	-0.55	$p < 0.01$	-0.30	$p < 0.05$
Amniotic fluid	-0.19	NS	-0.43	$p < 0.01$
Vitamin B <sub>12</sub>				
Serum	-0.21	NS	-0.16	NS
Amniotic fluid	-0.34	$p < 0.05$	-0.23	NS
Vitamin B <sub>6</sub>				
Whole blood	0.16	NS	-0.002	NS
Amniotic fluid	0.06	NS	-0.06	NS

NS, Not significant.

trations in plasma did not differ significantly. Twelve of 27 cases of the study group demonstrated total homocysteine concentrations in amniotic fluid exceeding the mean plus twice the SD of the control group (i.e.,  $>2.3 \mu\text{mol/L}$ ). The individual total homocysteine concentrations in amniotic fluid and plasma in both groups are shown in Fig. 1.

The mean amniotic fluid concentrations of folate and vitamins B<sub>12</sub> and B<sub>6</sub> did not significantly differ between the two groups (Table II). Similarly, none of the vitamins determined in blood were significantly different between the two groups.

In both groups the mean total plasma homocysteine

and whole blood vitamin B<sub>6</sub> concentrations were significantly higher than those of the corresponding amniotic fluid samples. Only in group 2 was a significantly lower mean amniotic fluid folate concentration found compared with the mean serum folate value. In groups 1 and 2 the mean vitamin B<sub>12</sub> levels of amniotic fluid were significantly higher than those in serum. There was no significant difference in the mean vitamin B<sub>6</sub> concentration in whole blood or amniotic fluid between groups 1 and 2. The mean vitamin B<sub>6</sub> concentrations in amniotic fluid and maternal blood did differ significantly within the groups.

Pearson's partial coefficients of correlation were cal-

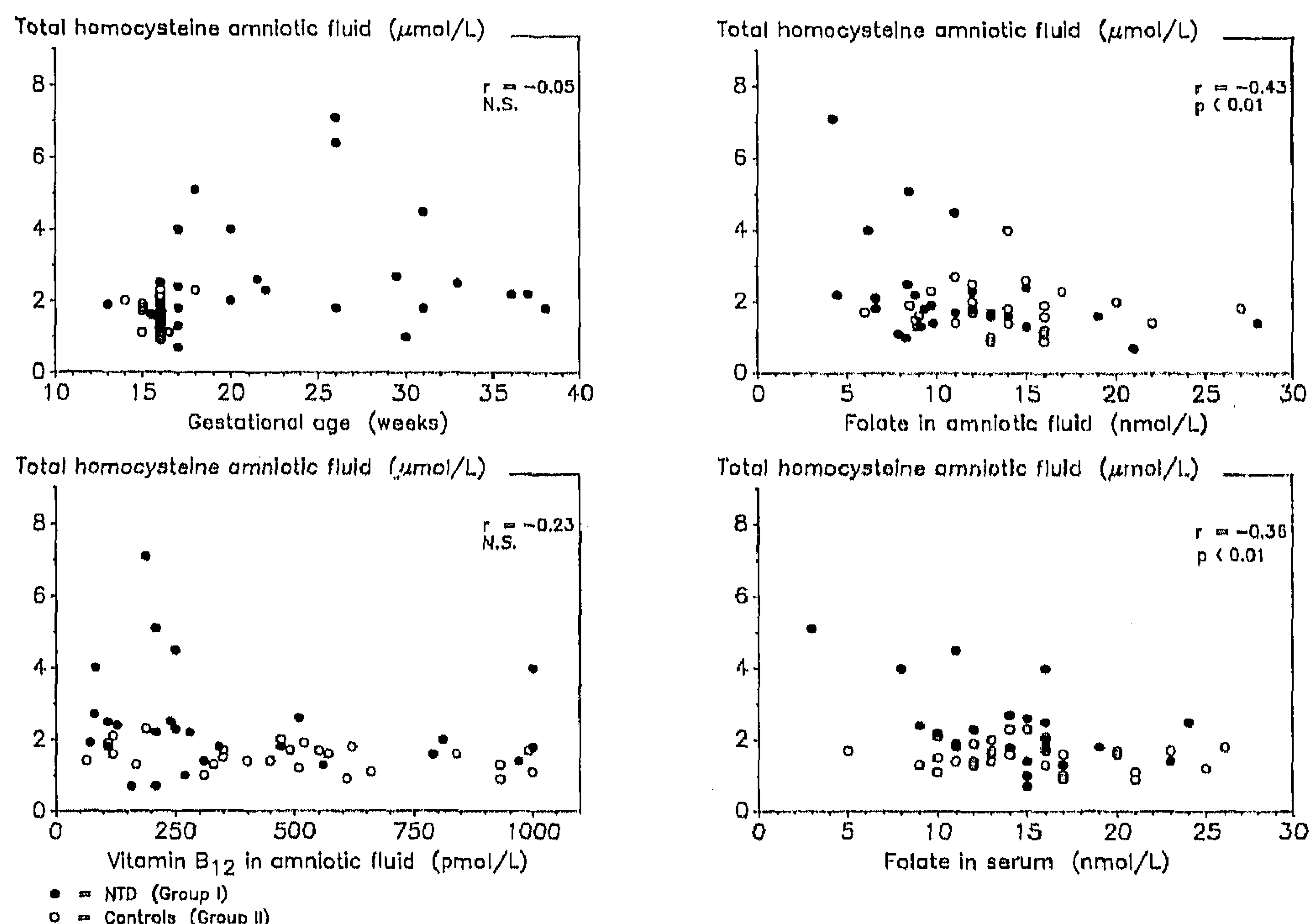


Fig. 2. Correlations of concentrations of total homocysteine in amniotic fluid with gestational age and vitamin B<sub>12</sub> in amniotic fluid and with folate in amniotic fluid and serum. NTD, Neural tube defect.

culated between total homocysteine, the various vitamin levels, and maternal and gestational age. Because the correlations appeared not to be significantly different between the groups and regression lines were parallel, correlation coefficients were calculated for both groups combined. The correlations are shown in Table III and Fig. 2. The total homocysteine concentrations in plasma and amniotic fluid were not significantly correlated with maternal age. Only plasma, not amniotic fluid total homocysteine concentrations, showed a significant inverse correlation with gestational age. Folate levels in maternal serum and red blood cells were significantly inversely correlated with total homocysteine in amniotic fluid. Also, vitamin B<sub>12</sub> in amniotic fluid and maternal plasma homocysteine levels did show a significant inverse correlation.

### Comment

This study demonstrates that pregnant women carrying a fetus with a neural tube defect (group 1) have significantly higher total homocysteine levels in amniotic fluid than do controls (group 2). However, plasma total homocysteine levels did not differ significantly between groups. Plasma levels of either group were lower than those of nonpregnant women (7.2 μmol/L in pregnant control women vs 9.8 μmol/L in nonpregnant women<sup>15</sup>), which is in accordance with other studies.<sup>15, 16</sup> This finding might be related to hemodilution, increased remethylation of homocysteine induced by en-

hanced demands for methionine by the fetus or to the impact of increased sex hormone levels during pregnancy on homocysteine metabolism.<sup>17, 18</sup>

The total homocysteine concentrations in amniotic fluid of both groups were significantly lower in amniotic fluid than in plasma, as has been demonstrated previously in normal pregnancies.<sup>15</sup> In the current study a significant positive correlation could be established between the total homocysteine concentrations in the two compartments (i.e., maternal plasma and amniotic fluid). The transplacental transfer of homocysteine may be an important determinant of the level of homocysteine in amniotic fluid. The report of Kurczynski et al.,<sup>19</sup> who first described an untreated homocystinuric pregnant woman with dramatically increased homocysteine concentration in amniotic fluid, is in accordance with this observation. However, it is not excluded that the increased homocysteine concentration in amniotic fluid is caused by a defective homocysteine metabolism or by leakage from the neural tube defect of the fetus into the amniotic fluid.

There was no significant correlation between total homocysteine in plasma or amniotic fluid and gestational or maternal age, with the exception of the inverse correlation between plasma total homocysteine and gestational age. Furthermore, it revealed from the study of Andersson et al.<sup>20</sup> that total plasma homocysteine is directly correlated with age. Therefore it is very unlikely that the significantly higher total homocysteine levels in



amniotic fluid of fetuses with a neural tube defect compared with healthy controls are a consequence of the higher gestational age or the lower maternal age at which amniocentesis took place for the study group.

Shojania<sup>21</sup> reported a progressive decline of serum and red blood cell folate and serum vitamin B<sub>12</sub> concentrations in pregnancy and hypothesized that this might be caused by increased fetal demands, blood volume expansion, and increased urinary excretion and by changes in maternal folate absorption and metabolism. In particular, changes in vitamin B<sub>12</sub> binders may contribute to the physiologic decrease of this vitamin in pregnancy.<sup>21</sup> Decreased blood levels of vitamin B<sub>6</sub> during pregnancy have also been described.<sup>22</sup>

Folate or vitamin B<sub>12</sub> deficiency results in increased homocysteine concentrations in blood and urine.<sup>8, 9</sup> A significantly negative correlation between plasma total homocysteine and serum and red blood cell folate was observed in this study, which is consistent with previous studies.<sup>6, 8, 11</sup> The mean folate concentrations in maternal serum and red blood cells and amniotic fluid of group 1 were not significantly different from those in group 2. Therefore the increased homocysteine levels in amniotic fluid of group 1 cannot solely be explained on the basis of lower folate concentrations.

Also serum vitamin B<sub>12</sub> concentrations were comparable in the neural tube defect group and control women and were revealed to be within the normal ranges as given earlier for women of comparable age.<sup>13, 23</sup> In both groups vitamin B<sub>12</sub> concentrations in amniotic fluid were significantly higher than those in serum. This is in line with the results of previous studies suggesting that there is an active transplacental transfer of this vitamin against a concentration gradient.<sup>13</sup>

Lower vitamin B<sub>12</sub> levels in amniotic fluid of normal pregnancies in women who previously had an infant with a neural tube defect have been determined in relation to increased amniotic fluid transcobalamin levels.<sup>24, 25</sup> This phenomenon is thought to be an indication of a genetic factor in the predisposition of neural tube defects. However, in our study the mean vitamin B<sub>12</sub> concentration in amniotic fluid was not significantly lower in the neural tube defect group compared with the control group.

To our knowledge, the presence of vitamin B<sub>6</sub> in human amniotic fluid has not been demonstrated before. In both groups the vitamin B<sub>6</sub> levels were significantly lower than in maternal blood. Its mean concentrations in maternal blood and amniotic fluid of the neural tube defect group were similar to the corresponding values of controls. No significant correlation between the concentrations of total homocysteine and vitamin B<sub>6</sub> in blood or amniotic fluid was found.

In conclusion, a significantly higher mean total homocysteine concentration was observed in amniotic

fluid of a pregnancy in which the fetus was affected with a neural tube defect compared with a control group. This might be the result of a primary or secondary derangement in maternal or fetal homocysteine metabolism, which is in line with our findings and earlier findings of others.<sup>5, 6, 26</sup>

We thank the participants who volunteered for this study. We also thank the prenatal diagnosis team in Nijmegen, Mrs. Y. Lawson, R. Fliervoet, and P. Hamel for practical assistance. We thank Mr. M. F. G. Segers, BSc, for his laboratory supervision; Mr. L.M.F. Geelen for expert technical assistance; Mrs. J.A.H. Droste, M.J.A. Leupers, J.M.P.M. van de Ven, and J. Beunk of the laboratory of endocrinology and reproduction; and Mrs. M.T.W.B. te Poele-Pothoff and A. De Graaf of the laboratory of pediatrics for technical assistance.

#### REFERENCES

- Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child* 1976;51:944-50.
- Schorah CJ, Smithells RW, Scott JM. Vitamin B12 and anencephaly [Letter]. *Lancet* 1980;1:880.
- Medical Research Council Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council vitamin study. *Lancet* 1991;2:132-7.
- Czeizel AE, Dudás I. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327:1832-5.
- Steegers-Theunissen RPM, Boers GHJ, Trijbels JMF, Eskes TKAB. Neural tube defects and derangement of homocysteine metabolism. *N Engl J Med* 1991;324:199-200.
- Steegers-Theunissen RPM, Boers GHJ, Trijbels JMF, et al. Maternal hyperhomocysteinemia: a risk factor for neural tube defects? *Metabolism* [In press].
- Mudd SH, Levy HL, Skovby F. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited diseases*. New York: McGraw-Hill, 1989;693-734.
- Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. *J Clin Invest* 1988;81:466-4.
- Hall CA, Chu RC. Serum homocysteine in routine evaluation of potential vitamin B<sub>12</sub> and folate deficiency. *Eur J Haematol* 1990;45:143-9.
- Kang S, Wong PWK, Susmano A, Sora J, Norusis M, Ruggie N. Thermolabile methylenetetrahydrofolate reductase: an inherited risk factor for coronary artery disease. *Am J Hum Genet* 1991;48:536-45.
- Brattström L, Israelsson B, Norrving B, et al. Impaired homocysteine metabolism in early-onset cerebral and peripheral occlusive disease—effects of pyridoxine and folic acid treatment. *Atherosclerosis* 1990;81:2004-6.
- Franken DG, Boers GH, Blom HJ, Trijbels JM. Effect of various regimens of vitamin B<sub>6</sub> and folic acid on mild hyperhomocysteinemia in vascular patients. *J Inher Metab Dis* 1994;17:159-62.
- Steegers-Theunissen RPM, Steegers EAP, De Boer R, Thomas CMG, Kloosterman MD, Eskes TKAB. Elevated folate levels in amniotic fluid after oral supplementation. *Eur J Obstet Gynecol Reprod Biol* 1990;36:283-8.
- Fiskerstrand T, Refsum H, Kvalheim G, Ueland PM. Homocysteine and other thiols in plasma and urine: automated determination and sample stability. *Clin Chem* 1993;39:263-71.



15. Kang SS, Wong PWK, Zhou J, Cook Y. Total homocysteine in plasma and amniotic fluid of pregnant women. *Metabolism* 1986;35:889-91.
16. Andersson A, Hultberg B, Brattström L, Isaksson A. Decreased serum homocysteine in pregnancy. *Eur J Clin Chem Biochem* 1992;30:377-9.
17. Boers GHJ, Smals AGH, Trijbels FJM, Leermakers AI, Kloppenborg PWC. Unique efficiency of methionine metabolism in premenopausal women may protect against vascular disease in the reproductive years. *J Clin Invest* 1983;72:1971-6.
18. Steegers-Theunissen RPM, Boers GHJ, Steegers EAP, et al. Effects of sub-50 oral contraceptives on homocysteine metabolism. *Contraception* 1992;45:129-39.
19. Kurczynski TW, Muir WA, Fleisher LD, et al. Maternal homocystinuria: studies of an untreated mother and fetus. *Arch Dis Child* 1980;55:721-3.
20. Andersson A, Brattström L, Israelsson B, Isaksson A, Hamfelt A, Hultberg B. Plasma homocysteine before and after methionine loading with regard to age, gender, and menopausal status. *Eur J Clin Invest* 1992;22:79-87.
21. Shojania AM. Folic acid and vitamin B12 deficiency in pregnancy and the neonatal period. *Clin Perinatol* 1984; 11:433-59.
22. Shane B, Contractor SF. Assessment of vitamin B6 status: studies on pregnant women and oral contraceptive users. *Am J Clin Nutr* 1975;28:739-7.
23. Economides DL, Ferguson J, Mackenzie IZ, Darley J, Ware II, Holmes-Siedle M. Folate and vitamin B12 concentrations in maternal and fetal blood, and amniotic fluid in second trimester pregnancies complicated by neural tube defects. *Br J Obstet Gynaecol* 1992;99:23-5.
24. Gardiki-Kouidou P, Seller MJ. Amniotic fluid folate, vitamin B<sub>12</sub> and transcobalamins in neural tube defects. *Clin Genet* 1988;3:441-8.
25. Magnus P, Magnus EM, Berg K. Transcobalamins in the etiology of neural tube defects. *Clin Genet* 1991;39:309-10.
26. Kirke PN, Molloy AM, Daly LE, et al. Maternal plasma folate and vitamin B<sub>12</sub> are independent risk factors for neural tube defects. *Q J Med* 1993;86:703-8.

---

## A new placental enzyme in the metabolism of cocaine: An in vitro animal model

Bertis B. Little, MA, PhD, Daniel A. Roe, MD, R. William Stettler, MD,  
Van R. Bohman, MD, Kim L. Westfall, MS, and Sohrab Sobhi, BS

Dallas, Texas

**OBJECTIVE:** The aim of this study was to analyze placental metabolism in a genetically controlled in vitro animal model.

**STUDY DESIGN:** Placentas from Sprague-Dawley rats were centrifuged, and microsomes were isolated. Four treatment groups were incubated with cocaine over four time periods: placental microsomes + cocaine, placental microsomes + diisopropyl fluorophosphate (an anticholinesterase) + cocaine, placental microsomes + cocaine + butyrylcholinesterase, and a blank (cocaine only). Gas chromatography was used to quantify cocaine (Limit of quantitation = 19 ng/ml) and metabolites. Gas chromatography/mass spectrometry was used to verify the identity of the metabolites.

**RESULTS:** Butyrylcholinesterase enhanced cocaine metabolism to ecgonine methyl ester. More than 40% of cocaine was metabolized to norcocaine by rat placenta when diisopropyl fluorophosphate suppressed cocaine. Norcocaine is produced by hepatic N-demethylase action on methyl-bearing nitrogen in cocaine, suggesting that placenta and liver have this capacity. Gas chromatography/mass spectrometry was essential to the identification of norcocaine, because norcocaine is frequently not identified.

**CONCLUSIONS:** This biotransformation of cocaine to norcocaine may be a primary metabolic pathway induced in the cholinesterase-deficient placenta. This has clinical implications because norcocaine is ninefold more active physiologically than cocaine or ecgonine methyl ester. (*AM J OBSTET GYNECOL* 1995;172:1441-5.)

**Key words:** N-demethylase, cholinesterase, cocaine, placenta, metabolism

*From the Division of Prenatal Diagnosis and Clinical Genetics, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center.*

*Received for publication June 27, 1994; revised November 2, 1994; accepted November 7, 1994.*

*Reprint requests: Bert Little, MA, PhD, Associate Professor, Division*

*of Prenatal Diagnosis and Clinical Genetics, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX 75235-9032.*

*Copyright © 1995 by Mosby-Year Book, Inc.  
0002-9378/95 \$3.00 + 0 6/1/61855*